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⑯ Stabilization of unstable drugs or food supplements.

⑯ A granulation method involving polysaccharide gelling agents, e.g., alginic acid, and a metal (especially magnesium) salt, oxide or hydroxide, e.g., magnesium hydroxide, is developed for the stabilization of heat- and/or moisture-sensitive drugs or food supplements such as Efrotomycin, avermectins, milbemycins, mocomycin and other drugs. It has been found that the granules so obtained can be incorporated into various formulations without substantial decomposition.

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STABILIZATION OF UNSTABLE DRUGS OR FOOD SUPPLEMENTS

The present invention relates to the stabilization of drugs including antibiotics and food supplements. More particularly, but not exclusively, it concerns the granulation of Efrotomycin, milbemycins, tylosin derivatives, e.g. A.I.V. (3-acetyl-4"-isovaleryl tylosin), antibiotics B-5050 and tetra-5 hydro-B-5050, Ivermectin, mocimycin and goldinomycin. The present invention is based on the discovery that the granules obtained by granulating such compounds in alginic acid and magnesium hydroxide exhibit unexpectedly enhanced stability and can be incorporated into various formulations without substantial decomposition. When the drugs or food 10 supplements are administered to animals, the formulations include animal feeds, pellets and feed premixes.

Efrotomycin (FR-02A) is a new antibiotic which also exhibits growth-promoting activity. It is effective against both gram-positive and gram-negative bacteria and accordingly is useful in the treatment of a broad spectrum of infections in animals. Efrotomycin is disclosed in U.S. Patent 4,024,251 issued 17 May 1977 to Maiese and Wax. The antibiotic is isolated from the fermentation broth of Streptomyces lactamfuran by solvent extraction and is believed to have the molecular structure as follows:

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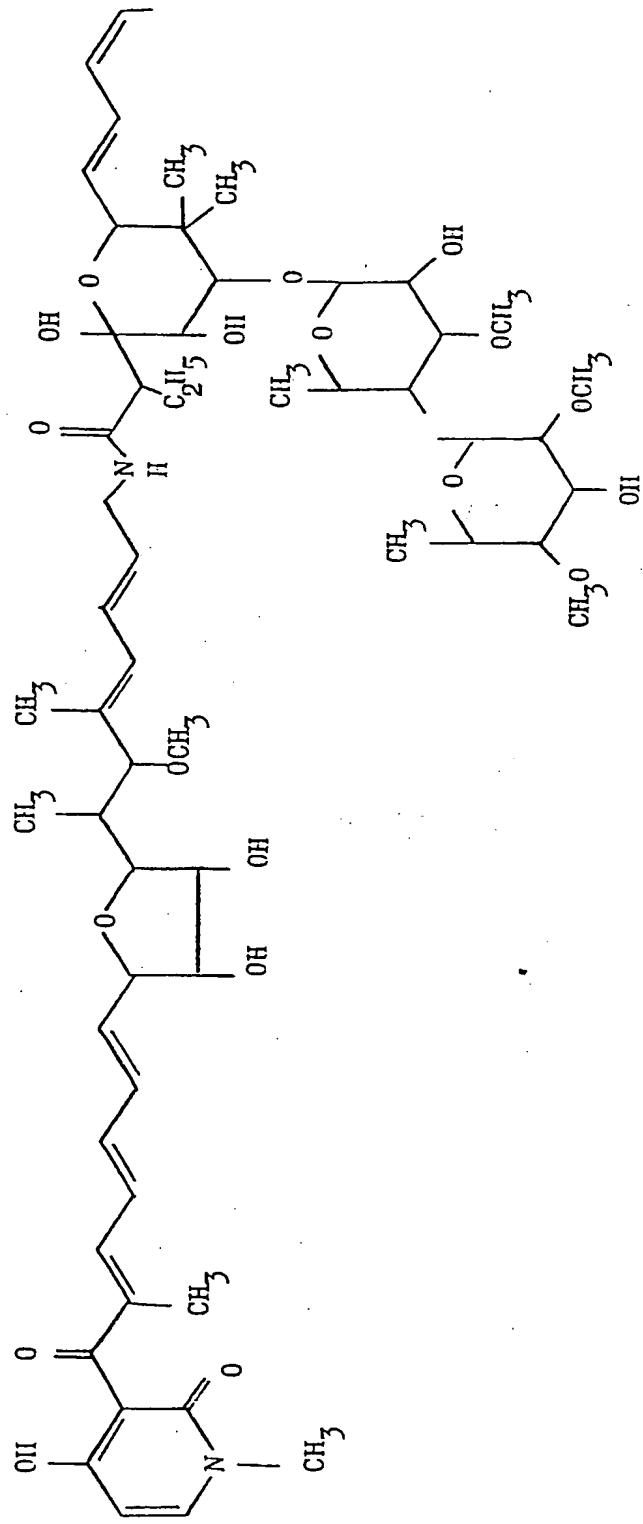
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The physical properties of Efrotomycin (FR-02A) are summarized as follows:

Elemental analysis:

C 60.98%

5 H 7.60%
N 2.60%

N 2,608

The corresponding empirical formula

$C_{59}H_{90}N_2O_{21}$ is consistent with monohydrated FR-02A. This is in agreement with a molecular weight of about 1168 of the sodium complex of FR-02A determined by field desorption mass spectrometry.

Further mass spectroscopic study of FR-02A determined the molecular weight 1144 for the uncomplexed compound corresponding to the empirical formula

15 $C_{59}H_{88}N_2O_{20}$

FR-02A as the ammonium salt is soluble in alcohol and chloroform. It is moderately soluble in water at pH 7.0 or higher. A U.V. spectrum of the ammonium salt in water showed:

20 max. 233 nm: $E_{1\text{cm}}^{1\%}$ = 320
max. 328 nm: $E_{1\text{cm}}^{1\%}$ = 180

After further purification FR-02A in the free acid form has the following U.V. spectrum in methanol - 0.05M phosphate buffer pH 6.85 (20:80):

25 max. 325 nm: $E_{1\text{cm}}^{1\%}$ = 317
 max. 230 nm: $E_{1\text{cm}}^{1\%}$ = 554
 max. 219 nm: $E_{1\text{cm}}^{1\%}$ = 556

Specific optical rotation of FR-02A sodium salt is $[\alpha]_D^{20} -56.6 \pm 0.5$ (C=1, MeOH)

30

The nuclear magnetic resonance spectrum of antibiotic FR-02A was obtained at 100 MHz with CDCl_3 as the solvent and tetramethylsilane (TMS) as the internal standard. Representative features of the spectrum were Doublets at 1.21(3H), 1.31(3H), 1.74(3H), 4.63(1H), 4.87(1H), 5.94(1H) and 7.32(1H) ppm. Overlapping signals of 4 other C-methyl groups centered at about 0.94 ppm; Singlets at 1.65(3H), 2.02(3H), 3.15(3H), 3.42(3H), 3.45(3H), 3.54(3H), and 3.58(3H) ppm.

The infrared absorption spectrum of antibiotic FR-02A in a Nujol mull exhibits characteristic absorption at the following wave lengths expressed in reciprocal centimeters:

15 Broad Band at: 3400
Strong bands at: 1640, 1460, 1380, 1080, 1020
Prominent bands at: 1550, 1505, 1240, 1195,
940, 860, 720, 620.

20 Further characteristics of FR-02A as well as the process for isolating the antibiotic are described in U.S. Patent 4,024,251 and are herein incorporated by reference.

25 Efrotomycin is found to be unstable at elevated temperatures especially in the presence of moisture and feed components. However, in administering Efrotomycin to animals, it is most convenient and economic to include the antibiotic-growth promotor agent in premixes for animal feeds. Usually a premix is blended into animal feeds 30 followed by injection of steam resulting in a final temperature of 85-100°C. The mixing process

takes about 2-15 minutes. The agglomerates may be either cooled and dried to produce a mash feed or extruded to give pelleted feed. In other words, Efrotomycin must be stabilized first before it can be 5 incorporated into animal feeds.

Accordingly, it is desirable to develop a method of formulation for the stabilization of Efrotomycin to enable the inclusion thereof in animal feed.

10 One of the commonly used methods of formulation for stabilization is granulation because of ease, efficiency and consequently lower cost. Methods described in the literature include granulation with specific inorganic materials (United States Patent 15 3,627,885, 14th December 1971) or with starch (United States Patent 4,048,268, 13th September 1977). Neither of these techniques were suitable for Efrotomycin.

20 Granulation with inorganic salts, particularly those of magnesium did result in some stabilization but unexpected synergistic improvement occurred when polysaccharides were incorporated into the formulation as can be seen from table 1.

25 Table 1. The effect of the addition of polysaccharide gelling agents to magnesium hydroxide on the stability of efrotomycin stored in animal feed at 50°C, (all contain 5% efrotomycin and magnesium hydroxide:gum in the weight ratio 1:1).

	<u>Polysaccharides</u>	<u>Magnesium hydroxide</u>	<u>Storage time</u>	<u>% of initial remaining</u>
5	--	--	17 days	12
	--	present	25 days	56
	Guar gum (anionic)	present	28 days	71
	Guar gum (nonionic)	present	28 days	79
	Guar gum (cationic)	present	28 days	55
10	Tragacanth	present	28 days	68
	Acacia	present	28 days	81
	Alginic acid	present	35 days	100
	Calcium alginate	present	56 days	82
	Sodium alginate	present	30 days	69
15	Maize starch	present	14 days	90
	Locust Bean gum	present	14 days	83
	Agar-agar	present	14 days	80

For efrotomycin incorporation of alginic acid gives the best stabilization although all the polysaccharides including those listed in Table 1 and xanthan gum, karaya gum, gum ghatti, and carrageenan offer significant protection.

In case of efrotomycin, the ratio of alginic acid to magnesium hydroxide is important as can be seen in table 2.

Table 2. The effect of alginic acid - magnesium hydroxide ratio on the stability of efrotomycin stored in animal feed at 50°C (all contain 10% efrotomycin).

	<u>% Magnesium hydroxide w/w</u>	<u>% Alginic acid w/w</u>	<u>% of initial remaining after 4 months storage</u>
5	90	-	26
	75	15	73
	60	30	91
	45	45	93
	30	60	100
	10	75	75
	-	90	37

It should be noted that the method of the present invention is not limited to Efrotomycin. Any other unstable animal drugs or food supplements may be incorporated into animal feeds or other formulations including human drug formulations according to the formula and process described herein. Particularly, for example, the following drugs:

20 (1) Ivermectin: a potent antiparasitic agent disclosed in U.S. Patent 4,199,569.

(2) Milbemycins (antibiotics B-41): antibiotics characterized in U.S. Patents 4,144,352; 3,950,360; and British Patent Specification No. 2,056,986.

25 (3) Tylosin and derivatives, e.g., A.I.V.: antibiotics disclosed in U.S. Patent 4,092,473. A.I.V. is the 3-acetyl-4"-isovaleryl derivative (R₁ is acetyl and R is isovaleryl in formula I) of tylosin.

(4) Antibiotics B-5050 and tetrahydro-B-5050: disclosed in U.S. Patent 3,853,842.

30 (5) Mocimycin and dihydromocimycin, antibacterial agents disclosed in U.S. Patents 3,927,211 and 4,062,948.

(6) Goldinomycin disclosed in U.S. Patent 3,657,421.

The physical characterization, the biological activity and the isolation of the above-identified drugs are disclosed in the above documents.

It has been found that these drugs may also be stabilized by granulation with a polysaccharide gelling agent especially alginic acid 5 blended with an inorganic salt, particularly metal oxides or hydroxides such as magnesium hydroxide. The granules may be incorporated into feed, tablets, capsules, or other formulations.

The present invention concerns a method of granulation for the stabilization of unstable or heat-sensitive animal drugs or food supplements, 10 such as Efrotomycin, tylosin and derivatives (A.I.V.), milbemycins, avermectins such as Ivermectin, mocimycin and goldinomycin. The granulation enables the incorporation of these drugs or food supplements into animal feeds or other formulations without substantial decomposition due to heat, 15 humidity, and other adverse conditions. By proceeding in accordance with the invention, and in particular the preferred embodiments set out below, it is possible to produce sufficiently stable granules for inclusion of unstable drugs or food supplements in animal feeds, or other human and animal formulations such as feed, tablet and capsules.

The stabilizing granulation formula of the present invention comprises:

- 20 (a) 0.1 to 70 parts by weight of an active compound especially Efrotomycin, A.I.V. or Ivermectin;
- (b) 10 to 80 parts by weight of a polysaccharide gelling agent especially guar gums (natural or synthetic), tragacanth, acacia, alginic acid and its salts and derivatives, starch, locust bean gum, agar-agar, xanthan gum, karaya gum, gum ghatti 25 and carrageenan or a mixture thereof; and

(c) 10 to 80 parts by weight of a metal salt especially an oxide, a hydroxide, a carbonate or a silicate of aluminum, calcium or magnesium, for example, magnesium hydroxide.

In a preferred embodiment, the formula comprises:

5 (a) 2-40 parts by weight of an active compound;

(b) 20-50 parts by weight of alginic acid; or calcium alginate or a combination thereof in the ratio 2-3 parts of alginic acid to 2-3 parts of calcium alginate; and

(c) 20-85 parts by weight of a metal oxide or hydroxide.

In the most preferred embodiment of this invention the formula comprises:

- (a) 5-35 parts by weight of an active compound;
- (b) 15-50 parts by weight of alginic acid; and
- 5 (c) 20-80 parts by weight of magnesium hydroxide.

Efrotomycin, while it is unstable in the below-described feeds and feed additives, does not appear to be unstable to water alone. Thus, the instant process is not a strict protection method 10 against hydrolysis. The instant formulation protects antibiotics against deterioration in the presence of feeds. Applicants do not wish to be bound by theory, but this may be accomplished by isolating the compound from the components of feed which cause the 15 deterioration. Thus any compound which is intended for use in feed or feed-like components, and which is unstable in such feeds or feed-like components, but otherwise stable under neutral conditions will benefit from the use of the process of this invention.

20 For preparing the above defined formulae, the active compound is mixed and agglomerated with other ingredients in the indicated amounts. A sufficient amount of a solvent, for example water; lower alkanol especially C₁₋₆ alcohol such as ethanol and methanol; 25 and lower alkanone especially C₁₋₆ alkanone such as acetone and diethylketone or a mixture thereof is added and thoroughly dispersed to obtain a wet mass of the desired consistency. Usually, the amount of the solvent needed is about 0.05 - 2 parts per part by 30 volume of the mixed ingredients. Subsequently, the wet blend is sieved, dried, and screened to yield granules

of desired sizes. Alternatively, the mixing can be carried out in a high speed mixer granulator followed by milling and drying in a fluidized bed.

5 Alternatively, the granulated product defined above may also be obtained by dry compression of the ingredients in the indicated amounts followed by subsequent grinding in order to get the granulated product. Alternatively, the mixed ingredients may be slurried with a suitable solvent and spray dried into
10 granules.

15 The amount of biologically active compound in the granules may be adjusted up to the most convenient range-e.g., from 0.1 percent to 70 percent by weight - for facilitating the dispersion of the compounds in the feed, and the resulting composition (granules) is then dispersed in any suitable feed, premix substrate or simply used as premix by itself. When the granules are dispersed in animal feed, it is usually incorporated at the rate of about 0.1-10 kg per ton preferably 0.5 - 2
20 kg per ton to achieve the desired dose.

25 Usually the wet-granulation technique is used, the active compound, for example, Efrotomycin, is thoroughly mixed in the indicated amount with alginic acid and magnesium hydroxide. An adequate amount of water or other solvent is added to obtain a wet mass of required consistency. The resulting agglomerate is then granulated by passing through a 16 mesh (1000 μm) screen and dried at about 30°-60°C, preferably at about 45°C for about 5-48 hours, usually about 15-20 hours.
30 Optionally, the granules may be rescreened through a 30 mesh (595 μm) or other suitable screen to obtain the required size.

Alternatively the mixing can be carried out in a high speed mixer granulator followed by milling and drying in a fluidized bed at about 30°C to 55°C for about 1-5 hours.

5 Although it is not required for performing the invention the formulation may be admixed with suitable inert diluents such as lactose, sucrose, calcium phosphate or micro-crystalline cellulose.

10 Disintegrating agents (e.g. starch or its modifications) or lubricants such as magnesium stearate, stearic acid, polyethylene glycol or talc may be added. The blend may be filled into capsules or compressed into tablets to allow the administration of stabilized drugs, e.g., Ivermectin, as a convenient

15 oral dose.

The following examples are intended to illustrate the preparation of compositions of the invention but they are not to be construed as limiting the scope thereof.

20

EXAMPLE 1

A wet blend was prepared from mixing the following components:

25 Efrotomycin (60% pure) 33.33 parts by weight
Alginic acid 13.33 parts by weight
Magnesium hydroxide 53.34 parts by weight
Water sufficient to granulate
The wet blend was sieved 16 mesh, dried at 45°C for 2 hours and then rescreened 30 mesh.

30 The dried granule was used as a "concentrate" which may then be blended with other inert ingredients,

5 .g., oiled rice hulls and then incorporated into animal feed at the rate of 0.5-2 kg per ton to achieve the appropriate dose. The stabilization of Efrotomycin was achieved in both the premix and feed as shown below in Table III.

TABLE III

10 Stability of unprotected and protected Efrotomycin (100 ppm) in feed and pelleted feed. (Concentrate contains 20% by weight Efrotomycin; mean \pm 1 std. deviation)

Storage Conditions	Efrotomycin Concentrate (60% pure)	Stability in pelleted feed (w/w % initial)	
		Stability in feed (w/w % initial)	Concentrate
2 wks	40°C	-	90.4 \pm 13.1
	50°C	-	87.3 \pm 13.3 80.7 \pm 11.8
20 17 days	40°C	22.1 \pm 4.5	-
	50°C	11.9 \pm 3.3	-
4 wks	40°C	16.5 \pm 6.3	75.0 \pm 8.1 88.5 \pm 5.7
	50°C	Trace	73.1 \pm 13.3 66.5 \pm 4.7
25 6 wks	40°C	10.5 \pm 3.2	74.6 \pm 4.2 98.2 \pm 10.2
	50°C	Trace	78.8 \pm 8.1 64.3 \pm 3.67
12 wks	40°C	-	106 \pm 12.7 75.0 \pm 8.1

30 Following substantially the same procedure as described above, but substituting for Efrotomycin used therein Ivermectin, there is prepared a stabilized concentrate of Ivermectin.

EXAMPLE 2

A wet blend was prepared from mixing the following components.

5 Efrotomycin (60% pure) 8.35 parts by weight
 Alginic Acid 18.33 parts by weight
 Magnesium hydroxide 73.32 parts by weight
 Water sufficient to granulate.

10 The wet blend was treated as described in Example 1
and the stabilization achieved in feed is shown below.

	Storage conditions	Stability in feed (w/w % initial)
15	4 wks 40°C	91.3 ± 7.9
	50°C	81.9 ± 8.7
	7 wks 40°C	89.8 ± 8.6
	50°C	72.1 ± 0.5
	12 wks 40°C	96.0 ± 9.6

20 Following substantially the same procedure as described above, but substituting for Efrotomycin used therein Ivermectin, there is prepared a stabilized concentrate of Ivermectin.

25 EXAMPLE 3

A wet blend was prepared by mixing the following components.

30 Efrotomycin 8.4 parts by weight
 Alginic acid 45.8 parts by weight
 Magnesium hydroxide 45.8 parts by weight
 Water sufficient to granulate

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The wet blend was treated as described in Example 1 and the stabilization in feed is shown below.

Storage Conditions	Stability in feed (% initial)
9 weeks at 50°C	99 ± 9

EXAMPLE 4

A wet blend was prepared by mixing the following components.

Efrotomycin	8.4 parts by weight
Calcium alginate	45.8 parts by weight
Magnesium hydroxide	45.8 parts by weight
Water	sufficient to granulate

The wet blend was treated as described in Example 1 and the stabilization in feed is shown below.

Storage Conditions	Stability in feed (w/w% initial)
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4 weeks at 50°C	83 ± 4
8 weeks at 50°C	82 ± 5

EXAMPLE 5

A wet blend is prepared by mixing the following components.

Efrotomycin	8.4 parts by weight
Calcium alginate	22.9 parts by weight
Alginic acid	22.9 parts by weight
Magnesium hydroxide	45.8 parts by weight
Water	sufficient to granulate

The wet blend is treated as described in Example 1.

EXAMPLE 6

A wet blend was prepared by mixing the following components.

Efrotomycin	8.4 parts by weight
Maize starch	45.8 parts by weight
Magnesium hydroxide	45.8 parts by weight
Water	sufficient to granulate

The wet blend was treated as described in Example 1 and the stabilization in feed is shown below.

Storage Conditions	Stability in feed (w/w ⁺ initial)
14 days at 50°C	90 \pm 8
28 days at 50°C	83 \pm 9
56 days at 50°C	67 \pm 8

EXAMPLE 7

A wet blend was prepared by mixing the following components.

Efrotomycin	8.4 parts by weight
Alginic acid	45.8 parts by weight
Magnesium oxide	45.8 parts by weight
Water	sufficient to granulate

The wet blend was treated as described in Example 1 and the stabilization in feed is shown below.

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Storage Conditions	Stability in feed (w/w% initial)
18 days at 50°C	94 \pm 2
56 days at 50°C	83 \pm 2
5 months at 50°C	82 \pm 4

EXAMPLE 8

A wet blend was prepared by mixing the following components.

10	Efrotomycin (60% pure)	33.33 parts by weight
	Alginic Acid	33.33 parts by weight
	Magnesium Hydroxide	33.33 parts by weight
	Water	sufficient to granulate

15 The wet blend was treated as described in Example 1 and the stabilization in feed is shown below.

	Storage Conditions	Stability (%)
20	<u>In Mash</u>	
	12 weeks at 37°C	93 \pm 6
	12 weeks at 37°C (Sodium Salt)	113 \pm 7

	<u>Pellets</u>	
25	12 weeks at 37°C	84 \pm 11
	12 weeks at 37°C (Sodium Salt)	93 \pm 8

EXAMPLE 9

30 A wet blend was prepared by mixing the following components.

Ivermectin	1 part by weight
Alginic acid	49.5 parts by weight
Magnesium hydroxide	49.5 parts by weight
Water	sufficient to granulate

The wet blend was treated as described in Example 1 and the stabilization in feed is shown below.

Storage Conditions	Stability in feed (w/w% initial)	Ivermectin	Protected Ivermectin
7 days at 40°C	90	-	
14 days at 40°C	82	-	
4 weeks at 50°C	-		85

EXAMPLE 10

A blend is prepared by mixing the following components.

Ivermectin	2 parts by weight
Alginic acid	32.5 parts by weight
Starch (Directly compressible)	32.5 parts by weight
Magnesium hydroxide	32.5 parts by weight
Magnesium stearate	0.5 parts by weight

The blend is then compressed on a suitable tablet machine to produce thin compacts which are then milled to produce granules of about 0.5 mm diameter. Alternatively the blend may be passed through a roller compacter followed by screening.

The granule is then incorporated into feed as described in Example 1.

EXAMPLE 11

A wet blend is prepared by mixing the following components.

A.I.V.	20 parts by weight
Alginic acid	40 parts by weight
Magnesium hydroxide	40 parts by weight
Water	sufficient to granulate

The wet blend is treated as described in Example 1.

EXAMPLE 12Preparation of Tablet Formulation

<u>Ingredient</u>	<u>Milligrams Per Tablet</u>
Ivermectin granule	1.5
Bone meal flour	300
Microcrystalline cellulose	500
Flavor	250
Dibasic calcium phosphate	739.5
Magnesium stearate	9

The active granule is blended with a portion of the dibasic calcium phosphate and then incorporated with the flavor, microcrystalline cellulose and bone meal flour. The mix is blended to ensure homogeneity of Ivermectin, the magnesium stearate added and mixing continued for 3 minutes before compression on a suitable machine. Each tablet contains 75 µg of Ivermectin.

EXAMPLE 13Preparation of Capsule Formulation

<u>Ingredient</u>	<u>Milligrams per Capsule</u>
5 Ivermectin granule as prepared in Example 9	10
10 Starch	109
10 Magnesium Stearate	1.0

15 The active ingredient, starch and magnesium stearate are blended together. The mixture is used to fill hard shell gelatin capsules of a suitable size at a fill weight of 120 mg per capsule.

EXAMPLE 14

20 Following the procedure of Example 1, a protected wet blend containing mocimycin was prepared. The protected wet blend was granulated and incorporated into mash or feed pellets containing 100 ppm of mocimycin. The stability was noted as follows (percentages of original after the indicated time period):

In mash	6 weeks	at 30°C	100%
	6 weeks	at 37°C	99%
30 In pellets	6 weeks	at 30°C	96%
	6 weeks	at 37°C	83%

The unprotected drug has a stability of less than 25% after 2 months at 37 C.

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EXAMPLE 15

Following the procedure of Example 1 a protected wet blend containing goldinomycin was prepared. The protected wet blend was granulated and incorporated
5 into feed. The stability is rated as follows:

Storage Conditions	Stability (%)
6 weeks at 37°C	97%

10

15

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CLAIMS

1. A stable granular formulation for administering a compound in feed or feed-like components, comprising:
 - (a) an effective amount of a compound that is unstable in such feed or feed-like components, but that is otherwise stable under neutral conditions;
 - (c) an effective amount of a polysaccharide gelling agent; and
 - (c) an effective amount of a metal salt, oxide or hydroxide.
2. A formulation as claimed in Claim 1, in which the compound (a) is Efrotomycin, Ivermectin, a milbemycin, tylosin, A.I.V., antibiotic B-5050, antibiotic tetrahydro-B-5050, mocimycin, dihydromocimycin or goldinomycin, or a combination of two or more of them.
3. A formulation as claimed in Claim 1 or 2 in which the amount of the compound is from 0.1 to 70% by weight of the granular formulation.
4. A formulation as claimed in Claim 1 or 2 in which the ratio of the components is:
 - (a) 0.1 to 70 parts by weight of the said compound;
 - (b) 10-80 parts by weight of one or a combination of polysaccharide gelling agents; and
 - (c) 10-80 parts by weight of a metal salt, oxide or hydroxide.
5. A formulation as claimed in Claim 4 in which the ratio is
 - (a) 2-40 parts by weight of the said compound;
 - (b) 20-50 parts by weight of polysaccharide gelling agent(s); and
 - (c) 20-85 parts by weight of metal salt, oxide or hydroxide.

6. A formulation as claimed in Claim 5 in which the ratio by weight is
 - (a) 5-35 parts of the said compound;
 - (b) 15-50 parts of polysaccharide gelling agent(s); and
 - (c) 20-80 parts of magnesium hydroxide.
7. A formulation as claimed in Claim 6 in which the ratio by weight is
 - (a) 5 parts of the said compound
 - (b) 47.5 parts of polysaccharide gelling agent(s); and
 - (c) 47.5 parts of magnesium hydroxide.
8. A formulation as claimed in any one of Claims 1 to 7 in which the polysaccharide gelling agent is alginic acid, calcium alginate, starch or a combination of two or more of them.
9. A process for preparing a stable granular formulation as claimed in Claim 1 that comprises
 - (1) preparing a wet blend of the components described in sections (a), (b) and (c) of Claim 1 by mixing with water, a lower alkanol, a lower alkanone or a mixture of two or more of them;
 - (2) drying the blend; and
 - (3) preparing granules of desired sizes from the blend.
10. A process as claimed in Claim 9 in which the component (a) is as defined in Claim 2.
11. A process as claimed in Claim 9 in which the component (a) is Efrotomycin, Ivermectin, A.I.V., mocimycin, or goldinomycin.
12. A process as claimed in any one of Claims 9 to 11 in which the ratio of the components is as defined in any one of Claims 4 to 7.
13. A process as claimed in any one of Claims 9 to 12 in which the polysaccharide gelling agent is alginic acid, calcium alginate, starch or a combination of two or more of them.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a granular formation according to any one of Claims 1 to 8.

15. A composition as claimed in Claim 15 in which the carrier is an animal feed and the compound in the granular formation is Efrotomycin, Ivermectin, A.I.V., mocimycin, or goldinomycin.